20504/83

FORM 1

558994

REGULATION 9

COMMONWEALTH OF AUSTRALIA

PATENTS ACT 1952-1979

APPLICATION FOR A STANDARD PATENT

WE, KLINGE PHARMA GmbH, a German Company,

APPLICATION ACCEPTED AND AMENDMENT

ACCEPTED 17.12.86

of Berg-am-Laim-Str. 129,8000 München 80, Federal Republic of Germany

hereby apply for the grant of a Standard Patent for an invention entitled:-

"1,1,2-TRIPHENYL-BUT-1-ENE DERIVATIVES"

which is described in the accompanying complete Specification.

Details of basic application:

Number: P32 39 610.4

Country: Federal Republic of Germany

Date: 26th October 1982

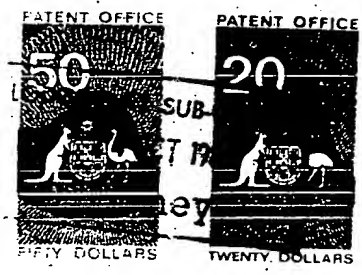
Our address for service is:- SHELSTON WATERS,
55 Clarence Street,
SYDNEY. N.S.W. 2000

DATED this 24th day of October, 1983.

KLINGE PHARMA GmbH

by

Fellow Institute of Patent Attorneys of Australia
of SHELSTON WATERS



LODGED AT SUB-OFFICE
24 OCT 1983
Sydney

To: The Commissioner of Patents,
WODEN. A.C.T. 2606.

File: D.B.122E

Fee: $94.00
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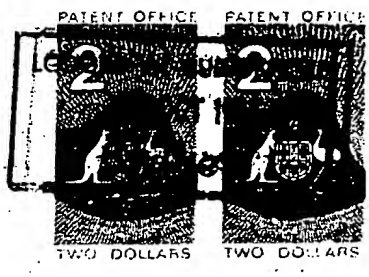

(CONVENTION – Company) FORM 8 – REGULATION 12 (2)

COMMONWEALTH OF AUSTRALIA PATENTS ACT, 1952-1973

20504/83

DECLARATION IN SUPPORT OF A CONVENTION APPLICATION FOR A PATENT

In support of the Convention Application No. 20504/83 made by [a] KLINGE PHARMA GmbH

(hereinafter referred to as "Applicant") for a patent for an invention entitled:

[b] "1,1,2-TRIPHENYL-BUT-1-ENE DERIVATIVES"

I, [c] Gunther Klinge

of [d] Berg-am-Laim-Str. 129, 8000 MUNCHEN 80, WEST GERMANY

do solemnly and sincerely declare as follows:

1. I am authorised by Applicant to make this declaration on its behalf.

2. The basic Application(s) as defined by section 141 of the Act was/were made in [e] WEST GERMANY on the 26 day of October, 1982 on the day of 19 by [f] KLINGE PHARMA GmbH

3. [g] HELMUT SCHICKANEDER, of Moosacker 25, D.8501 Eckental-Eckenhaid; ROLAND LOSER, of Fichtenweg 12, D-8133 Feldafing and HELMUT GRILL, of Zugspitzstrasse 148, D-8011 Vaterstetten, all West Germany, respectively is/are the actual Inventor(s) of the invention and the facts upon which Applicant is entitled to make the Application are as follows:

Applicant is the Assignee of the said Inventor(s).

4. The basic Application(s) referred to in paragraph 2 of this Declaration was/were the first Application(s) made in a Convention country in respect of the invention, the subject of the Application.

DECLARED at München, WEST GERMANY

this 10th day of January 19 84

[h] .....

(Signature of Declarant)

To THE COMMISSIONER OF PATENTS.

[a] Here insert (in full) Name of Company.

[b] Here insert Title of Invention.

[c] and [d] Here insert Full Name and Address of Company Official authorised to make declaration.

[e] Here insert Basic Country or Countries followed by date or dates of Basic Application(s).

[f] Here insert Full Name(s) of Applicant(s) in Basic Country.

[g] Here insert (in full) Name and Address of actual Inventor or Inventors.

[h] Personal Signature of Declarant (c) (no seal, witness or legalisation).

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(12) AUSTRALIAN PATENT ABRIDGMENT
(19) AU (11) AU-B-20504/83

(54) 1,1,2-TRIPHENYL-BUT-1-ENE DERIVATIVES

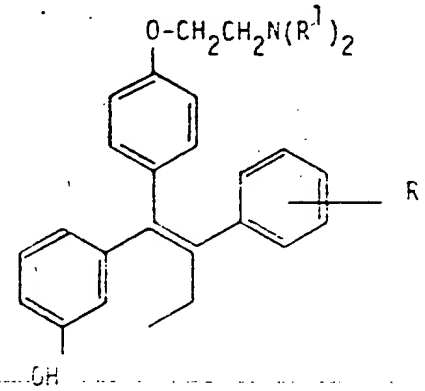
(71) KLING PHARMA GmbH
(21) 20504/83 558994 (22) 24.10.83
(24) 26.10.82
(31) 3239610 (32) 26.10.82 (33) DE
(43) 3.5.84 (44) 19.2.87
(51)[3] C07C 93/06 A61K 31/135 C07C 200/00

(72) HELMUT SCHICKANEDER. ROLAND LOSER AND HELMUT GRILL
(74) SW

(56)
33190/78	515458	C07C, A61K
39006/78	524339	C07C, C07D
856631/82	550530	C07C, A61K

(57) Claim

1. 1,1,2-triphenyl-but-1-ene derivatives of the general formula (1)



(1)

in which R is in position 3' or 4' and represents a methyl group, methoxygroup, hydroxy group or a halogen atom and R^1 represents a lower alkyl group; and therapeutically acceptable salts thereof.

558994

FORM 10

COMMONWEALTH OF AUSTRALIA

PATENTS ACT 1952-69

COMPLETE SPECIFICATION

FOR OFFICE USE:

Class Int. Class

Application Number: 20504/83

Lodged:

Complete Specification Lodged:

Accepted:

Published:

Priority:

Related Art:

This document contains the amendments made under Section 49.

and is correct for printing.

Name of Applicant: KLING PHARMA GmbH

Address of Applicant: BERG-AM-LAIM-STR. 129,8000 MÜNCHEN 80, FEDERAL REPUBLIC OF GERMANY

Actual Inventor: HELMUT SCHICKANEDER; ROLAND LÖSER and HELMUT GRILL

55

Address for Service: Shelston Waters. 168 Clarence Street, Sydney

Complete Specification for the Invention entitled: "1,1,2-TRIPHENYL-BUT-1-ENE DERIVATIVES"

The following statement is a full description of this invention, including the best method of performing it known to me/us:—

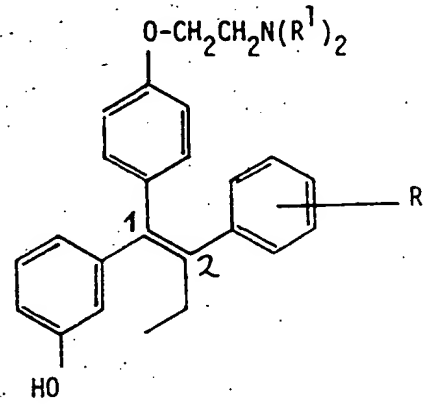
This invention relates to new 1,1,2-triphenyl-but-1-ene derivatives which possess valuable therapeutically-applicable properties.

From British Patent Specification 1 013 907 it emerges that 1,1,2-triphenyl-alkene derivatives can possess anti-oestrogenic properties and therefore they come into consideration for treatment of hormone-dependent tumors. One of them, (Z)-1-[4'-(2-dimethylaminoethoxy)phenyl]-1,2-diphenyl-but-1-ene (Tamoxifen, INN rec.) has already proved good in the therapy of hormone-dependent mammary tumors.

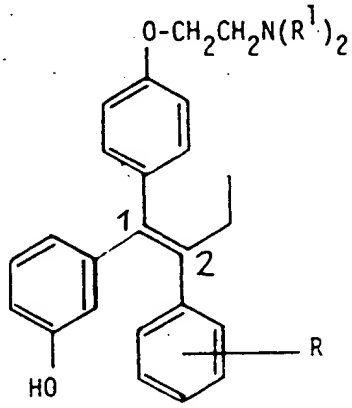
In German Offenlegungsschrift (DE-OS) 2 807 599 it has been established that a metabolite of Tamoxifen, (Z)-1-[4'-dimethylaminoethoxy)phenyl]-1-(4'-hydroxyphenyl)-2-phenyl-but-1-ene displays similar strong anti-oestrogenic activity. This holds true also for a number of (Z)-1-[4'-2-dimethylamino-ethoxy)-phenyl]-1-(4'-hydroxyphenyl)-2-phenyl-but-1-ene derivatives as described in European Application 0 002 097. From German Offenlegungs-schrift (DE-OS) 3 046 719 it emerges that (E)-1-[4'-(2-alkylaminoethoxy) phenyl] -1-(3'hydroxyphenyl)-2-phenyl-but-1-enes also possesses marked anti-oestrogenic properties.

In a highly specific test procedure it has been ascertained that a number of new 1,1,2-triphenyl-but-1-ene derivatives are clearly superior to Tamoxifen in their anti-oestrogenic effect. As shown below, compounds of the general formula (1) inhibit the growth of mammary tumor cells much more strongly than Tamoxifen. This is in keeping with their stronger binding affinity to oestrogen receptors.

The invention concerns 1,1,2-triphenyl-but-1-ene derivatives of the general formula (1), whose configuration corresponds to the E-form:



E-Form



Z-Form

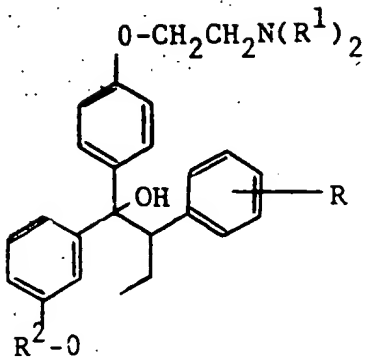
(1)

in which R in position 3' or 4' represents a methyl group, methoxy group, hydroxy group or a halogen atom and R^1 represents a lower alkyl group. The lower alkyl group can contain 1-4 C-atoms, preferably 1-3 C-atoms.

In this specification, the terms E-Form and Z-Form (E = "entgegen" meaning "across"), Z = "zusammen" meaning "together") refer to the position of the 3'-hydroxyphenyl group (priority 1 on the C-atom 1) relative to the position of the substituted phenyl group (priority 1 on C-atom 2) on the double bond in the butene chain [Nomenclature rule: R.T. Morrison, R.N. Boyd, Lehrbuch der Organischen Chemie, Verlag Chemie, page 167 (1974)].

The E- and Z-forms are clearly distinguished in their proton resonance signals of the dialkylamino group and the $O-CH_2$ group in the $-O-CH_2CH_2N(CH_3)_2$ side chain. The signals of the E-form in the claimed compounds are shifted to higher values compared to the Z-form. [D.J. Collins, J.J. Hobbs and C.W. Emmers, J. Med. Chem. 14,952 (1971)].

The invention also concerns a process for production of compounds of general formula (1) characterised in that carbinols of the general formula (2)



(?)

in which R in position 3' or 4' can be a methyl group, methoxy group, acetoxy-or an easily hydrolysable group or a halogen atom, R^1 can be a lower alkyl group, and R^2 represents an easily-hydrolysable protective group, are dehydrated in a manner known *per se* by the action of mineral acid, elimination of the protective group, the E-form is isolated from the resulting pair of isomers and optionally it is converted to a therapeutically acceptable salt.

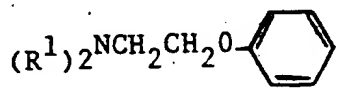
R is preferably a tetrahydropyranyloxy group.

R^2 is preferably the tetrahydropyranyl residue. The elimination of the protective group and the dehydration is achieved successfully with mineral acid in an alcoholic medium, preferably in ethanolic hydrochloric acid solution. The separation of the pair of isomers can be carried out by crystallisation or by chromotographic methods. According to solubility, the free bases or acid-addition salts are used for separation.

The starting materials needed for synthesis of the compounds according to the invention can be produced by the following process, for example:

By reaction of potassium phenylate with 2-chloroethyl-

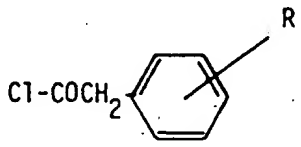
N,N-dialkyl-ammonium chloride at elevated temperature in ethanolic caustic potash solution and conversion of the reaction product into the hydrochloride, compound (3) is obtained:



$$(R^1)_2NCH_2CH_2O- \quad \times HCl \qquad (3)$$

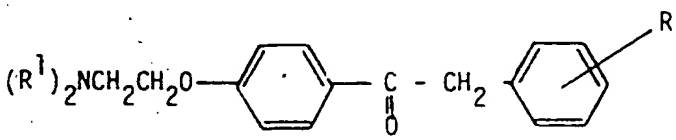
in which R^1 has the same meaning as in Formula (2).

In a Friedel-Crafts Reaction of compound (3) with substituted phenylacetyl chlorides of the general formula (4)



(4)

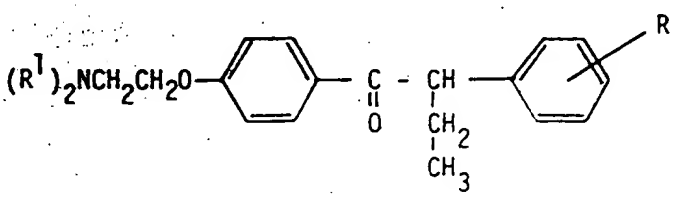
in which R in position 3' or 4' can be a methyl group, methoxy group, acetoxy group or a halogen atom, ethanones of general formula (5) are obtained



(5)

in which R has the same meaning as in formula (4) and R^1 has the same meaning as in formula (2).

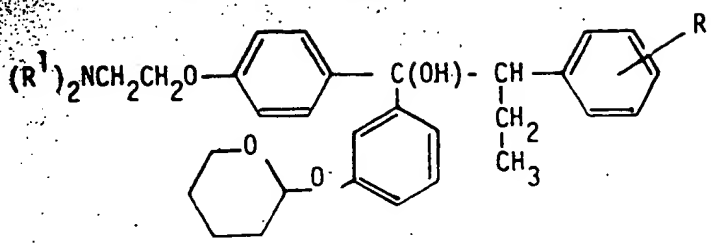
Compounds of the general formula (5) are converted with ethyl bromide in dimethyl formamide in the presence of sodium hydride to substituted butanones of the general formula (6)



(6)

in which R has the same meaning as in formula (4) and R^1 has the same meaning as in formula (2).

Compounds of general formula (6) react in anhydrous tetrahydrofuran with 3'-(2-tetrahydropyranyloxy)-phenyl magnesium bromide to diatereomeric carbinols of the general formula (7)



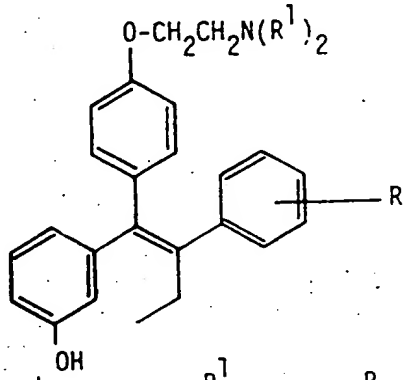
(7)

in which R has the same meaning as in formula (4) and R^1 has the same meaning as in formula (2).

Compounds of general formula (7) cleave off the tetrahydropyranyl residue in the presence of mineral acid even at room temperature in alcoholic solution and are converted by heat, with dehydration and optionally with elimination of a further protective group, to a pair of isomers, from which the E-isomer in its salt form or its base form can be isolated, so that compounds of general formula (1) in accordance with claim 1 can be obtained.

The following compounds support the claims:

Table 1



(1)

Compound No.	R^1	R	Melting Point °C (1)	
1	$-CH_3$	3'-CH_3	169	(a)
2	$-CH_3$	4'-CH_3	168	(a)
3	$-CH_3$	4'-OCH_3	133 to 134	(a)
4	$-CH_3$	3'-OH	186	(b)
5	$-CH_3$	4'-Cl	161 to 162	(a)
6	$-CH_3$	4'-Br	169 to 170	(a)
7	$-C_2H_5$	4'-OCH_3	128 to 130	(c)

(1) Crystallised from : (a) acetone (b) ether/petroleum ether (c) acetonitrile

The superiority of the claimed compounds is substantiated clearly in highly specific test procedures.

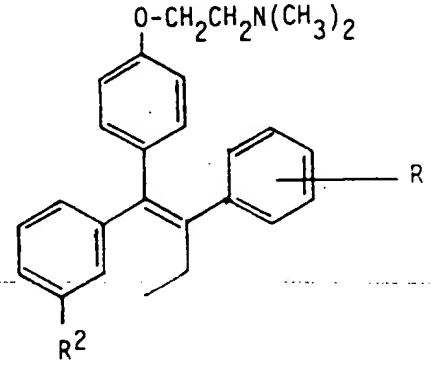
a) Binding affinity to oestradiol receptors

The measurement of binding affinity to oestradiol receptors is carried out according to the method of N. Devleeschouwer, G. Leclercq, A. Danguy and J.C. Heuson [Europ. J. Cancer, 14, 821 - 723 (1978)].

The uterus cytosol of female prepubertal white 2 kg heavy rabbits (New Zealand type) was incubated for 8 hours at $4^{o}C$ with 2.5×10^{-9} M [^{3}H]-oestradiol as well as with addition of unlabelled oestradiol (control) or test substances at various concentrations. The binding affinity to the oestradiol receptor is expressed as the concentration of unlabelled oestradiol (control) or test substance added to the uterus cytosol which achieved a 50 percent displacement of the [^{3}H]- oestradiol bound to the oestradiol receptor.

Table 2

Binding affinity of the test substances



Compound	R^2	R	$ED_{50\%}$ [M] *
Oestradiol (Control)			1.8×10^{-9}
Tamoxifen	H	H	2.5×10^{-7}
1	OH	3'-CH_3	3.5×10^{-8}
2	OH	4'-CH_3	7.3×10^{-8}
3	OH	4'-OCH_3	2.8×10^{-8}
5	OH	4'-Cl	8.5×10^{-8}

* Molar concentration of the substance which displaces 50% [^{3}H]-oestradiol from the oestradiol receptor.

The affinity of the claimed compounds for the oestradiol receptor is 3 to 9 times higher than with Tamoxifen.

b) Inhibition of RNA synthesis in isolated human breast tumor cells

Some years ago, it became possible to isolate oestrogen receptor positive [ER +] breast tumor cells from patients and to grow them continuously *in vitro*. These so-called Cell Lines contain almost all the morphological characteristics and metabolic activities observed *in vivo*. Therefore they represent an ideal model for testing anti-oestrogens, as direct statements can be made about the influence on the cell types to be treated *in vivo*.

To test anti-oestrogenic properties of the claimed compounds, oestrogenic receptor positive human breast tumor cells of the cell line ZR-75-1 were used, as described by Engel, L.W. et al [Linda W. Engel et al, Cancer Research 38, 3352 - 3364 (1978)]. The influence of the claimed compounds on the growth of these cells was monitored by the incorporation of labelled uridine or thymidine according to the method of Lippmann, M. et al. [Marc Lippmann et al, Cancer Research 36, 4595 - 4601 (1976)].

ZR-75-1 cells were incubated with Tamoxifen or with one of the claimed compounds for 48 hours in concentrations of 4×10^{-6}[M] to 1×10^{-7}[M], then mixed with labelled uridine or thymidine and after one hour the incorporation rate of the labelled material into the cells was determined. Table 3 shows the percentage inhibition of the cellular RNA-synthesis by the claimed compounds in comparison to Tamoxifen.

To imitate conditions *in vivo* the potency of the anti-oestrogenic effect of the claimed compounds was tested in the presence of an oestrogen.

ZR-75-1 cells were mixed simultaneously with one of the claimed compounds in a concentration of 1×10^{-6} [M] and with 17-β-oestradiol (1×10^{-8}[M]), after incubation for 48 hours labelled uridine or thymidine was added and after one hour the rate of incorporation of the labelled material into the cells was determined (Table 4).

Table 3

Percentage inhibition of RNA-synthesis in ZR-75-1 cells, in comparison with Tamoxifen.

	Concentrations of Substance		
	4×10^{-6} [M]	1×10^{-6} [M]	1×10^{-7} [M]
Compound No.	Percentage Inhibition		
1	100	74	47
Tamoxifen	100	44	29
2	100	62	42
Tamoxifen	100	39	16
3	100	68	36
Tamoxifen	99	43	13
4	100	73	33
Tamoxifen	100	44	29
5	100	61	41
Tamoxifen	100	39	16
6	100	70	47
Tamoxifen	100	59	43
7	91	37	4
Tamoxifen	93	46	2

As appears from Table 3, the claimed compounds inhibit RNA-synthesis in ZR-75-1 cells much more strongly from a dilution of 1×10^{-6} [M] than Tamoxifen which has been taken as the comparative substance in each of the tests concerned.

Table 4

Percentage inhibition of RNA-synthesis in ZR-75-1 cells

	Concentrations of Substance		
	Compound 1×10^{-6} [M]	Compound + 17-β-oestradiol 1×10^{-6} [M]	1×10^{-8} [M]
Compound No.	Percentage Inhibition		
1	74	74	
2	62	58	
3	68	65	
4	73	79	
6	70	74	
7	37	41	

As appears from Table 4, the claimed compounds inhibit the RNA -synthesis in ZR-75-1 cells unhindered also in the presence of a relatively high concentration of 17-β-oestradiol.

The compounds according to the invention therefore represent a valuable enrichment of the stock of medicines and can be used for treatment of malign breast tumors.

The invention also concerns medicines which contain a compound of general formula (1) as active ingredient as well as conventional pharmaceutical carriers and adjuvants.

The claimed compounds are preferably administered orally. Usually the oral dose amounts to 0.01 to 0.2 g, preferably 0.02 to 0.1 g. Nevertheless it can under certain circumstances be necessary to deviate from the above doses, depending upon the individual behaviour with respect to the medicament or the kind of formulation and the point of time or the interval at which the administration takes place. Thus it can be sufficient in some cases to manage with less than the above minimum amount, while in other cases the above-mentioned upper limit must be exceeded. In the case of application of larger amounts, it can be advisable to divide these into several individual doses through the day. The active ingredient can be made up in conventional form for oral administration e.g. in capsules, as tablets or as dragees The release of the claimed compounds can be accelerated or delayed according to pharmaceutical adaptation.

By mixing with solid powdery carriers such as micronised cellulose, potato starch or maize starch, with additives such as sodium citrate or calcium carbonate and binders such as polyvinyl pyrrolidone, gelatine or cellulose derivatives, optionally with addition of lubricants such as magnesium stearate, sodium lauryl sulphate or polyethylene glycols, they can be worked up into tablets or to dragee cores. Obviously with the oral administration forms, flavour adjusting agents can be added.

Two-part capsules, e.g. of hard gelatine, as well as closed soft gelatine capsules with a softener such as e.g. glycerine are suitable as other forms of administration. The push-together capsules contain the active ingredient preferably as a granulate e.g. mixed with fillers such as lactose, saccharose, mannite, starches such as e.g. potato starch or amylopectin, celluose derivatives or highly dispersed silicates. In soft gelatine capsules the active ingredient is dissolved or suspended in suitable fluids, e.g. in plant oils or in fluid polyethylene glycols.

The production of the starting materials is carried out according to known processes, such as described in part in German Patent Specification (DE - PS) 3 046 719.

Production of the starting materials.

a) N,N-dimethyl-2-phenoxyethyl ammonium chloride.

117 g (1.8 Mol) potassium hydroxide and 94.1 g (1.0 Mol) phenol were dissolved in 500 ml ethanol, mixed with a suspension of 144 g (1.0 Mol) 2-chloroethyl-N,N-dimethyl ammonium chloride in 500 ml ethanol and heated with vigorous stirring for 1 hour under reflux. After cooling the product is drawn off from the precipitated potassium chloride, post-washed with ethanol and the filtrate is concentrated under vacuum to dryness. The residue is taken up with ether, washed several times with 10 percent caustic soda solution, and then with water, and dried over sodium sulphate. By introduction of dry hydrogen chloride N,N-dimethyl-2-phenoxyethyl ammonium chloride is obtained, which can be recrystallised from isopropanol. Colourless crystals of melting point 163°C.
Yield 104.7 g.

b) 1-[4'-2-dimethylaminoethoxy) phenyl] -2-(subst. phenyl)-ethan-1-one.

20.1 g (0.1 Mol) N,N-dimethyl-2-phenoxyethyl ammonium chloride and 0.12 Mol of a corresponding substituted phenyl acetyl chloride in 1 l dichloromethane are mixed in portions with 24.7 g (0.18 Mol) anhydrous aluminium chloride at room temperature with vigorous stirring, then warmed slowly and heated for 2 hours under reflux. After cooling the mixture is poured onto ice, 100 ml concentrated hydrochloric acid is added thereto, separation is effected and the organic phase is agitated twice more with 10 percent hydrochloric acid. The united aqueous solutions are made alkaline and extracted three times with 200 ml ethyl acetate each time. After washing with water and drying over sodium sulphate the solvent is distilled off under vacuum and the resulting 1-[4'-(2-dimethylaminoethoxy) phenyl] -2-(subst. phenyl)-ethan-1-one is re-crystallised out of petroleum ether.

c) 1- [4'-(2-dimethylaminoethoxy)phenyl] -2-(subst.phenyl)-butan-1-one

The preparation is carried out by reaction of a corresponding 1- [4'-2-dimethylaminoethoxy)phenyl] -2-(subst. phenyl)-ethan-1-one with ethyl bromide and sodium hydride in anhydrous dimethyl formamide as described in detail in German Patent Specification (DE-PS) 3 046 719 (Example 1b).

d) 1- [4'-(2-dimethylaminoethoxy)phenyl] -2-(subst. phenyl-
1- [3'-(2-tetrahydropyranyloxy)phenyl]-butan-1-ol (Diastereomers)

The preparation is carried out by reaction of the 1- [4'-(2-dimethylaminoethoxy)phenyl] -2-(subst. phenyl)butan-1-one with 3'-(2-tetrahydropyranyloxy)phenyl magnesium bromide in anyhydrous tetrahydrofuran, as described in detail in German Patent Specification (DE-PS) 3 046 719 (Example 1e).

The claimed process is described in more detail below by way of production Examples.

Example 1

Production according to the invention of
(E)-1- [4'-(2-dimethylaminoethoxy)phenyl] -1-(3' ydroxyphenyl)-2-(4'-methoxyphenyl)-but-1-ene (Compound No. 3).

51.9 g (0.1 Mol) of the diastereomer mixture of 1- [4'-(2-dimethylaminoethoxy)phenyl] -2-(4'-methoxyphenyl)-1- [3'-(2-tetrahydropyranyloxy) phenyl] -butan-1-ol in 1.5 l ethanol are mixed with 60 ml concentrated hydrochloric acid and heated for 2 hours under reflux. Then the solvent is removed under vacuum, and the residue is suspended in 200 ml dilute ammonia solution and agitated twice with 250 ml ethyl acetate each time. The organic phase is washed to a neutral state with water and after drying over sodium sulphate the solvent is removed under vacuum. The residue is crystallised out of acetone. Colourless crystals of melting point 133 - 134°C; R_f 0.35 $CHCl_3/CH_3OH$ (7/3) ; yield 8.34 g (20%).

$C_{27}H_{31}NO_3$ (417.5)	Calculated	C 77.66	H 7.48	N 3.36
	Found	C 77.45	H 7.52	N 3.31

Molecular Weight 417 (determined by mass spectrometry)

IR-Spectrum (KBr) γ(O-H) 3650 to 2600 cm^{-1}

^{1}H-NMR-Spectrum * ($CDCl_3$) :

0.90	t (3)	$\underline{CH}_3$	[J=7.0]
2.33	s (6)	$(\underline{CH}_3)_2N$	
2.43 to 2.87	m (4)	$\underline{CH}_2$ and $\underline{CH}_2N$	
3.63 to 4.10 and 3.80	t (5) s	$\underline{CH}_2O$ and $\underline{CH}_3O$	
5.23 wide	s (1)	$\underline{OH}$ [interchangeable with D_2O]	
6.33 to 7.47	m (12)	Aromatics-$\underline{H}$	

* Taken at 60 MHz; the chemical shifts are given in ppm against TMS (=0.0), the relative intensities are enclosed in brackets. s = singlet; d = doublet; t = triplet; m = multiplet; J = coupling constant in Hz. δ = 0.0.

Example 2

Production according to the invention of (E)-1-[4'-(2-dimethylaminoethoxy)phenyl] -1,2-bis-(3'-hydroxy-phenyl)-but-1-ene (Compound No. 4)

58.9 g (0.1 Mol) of the diastereomer mixture of 1-[4'-(2-dimethylaminoethoxy)phenyl] -1,2-bis-[3'-2(tetrahydropyranyloxy)-phenyl] -butan-1-ol in 1 l 95 percent ethanol is mixed with 30 ml concentrated hydrochloric acid, then heated for 2 hours under reflux and worked up as in Example 1. Colourless light-sensitive crystals of melting point 186°C [ether/petroleum ether 1/1)] ; R_f 0.20 [$CHCl_3/CH_3OH$ (7/3)] ; yield 24.2 g (60%).

$C_{26}H_{29}NO_3$ (403.5)	Calculated	C 77.39	H 7.24	N 3.47
	Found	C 77.53	H 7.39	N 3.44

Molecular Weight 403 (determined by mass spectrometry)

IR-Spectrum (KBr) γ(OH) 3600 to 2300 cm^{-1}

^{1}H-NMR-Spectrum (d_6-DMSO) :

0.83	t	(3)	$\underline{CH}_3$	[J=7.0]
2.17	s	(6)	$(\underline{CH}_3)_2N$	
2.33 to 2.73	m	(4)	$\underline{CH}_2$ and $\underline{CH}_2N$	
3.90	t	(2)	$\underline{CH}_2O$	[J=6.0]
6.40 to 7.43	m	(12)	Aromatics-$\underline{H}$	
9.33 wide	s	(2)	$O\underline{H}$ [interchangeable with D_2O]	

Example 3

Production according to the invention of (E)-2-(4'-bromophenyl)-1-[4'-(2-dimethylaminoethoxy)phenyl]-1-(3'-hydroxyphenyl)-but-1-ene (Compound No. 6).

56.8 g (0.1 Mol) of the diastereomer mixture of 2-(4'-bromophenyl)-1-[4'-(2-dimethylaminoethoxy)phenyl]-1[3'-(2-tetrahydropyranyloxy)-phenyl]-butan-1-ol in 500 ml ethanol are mixed with 25 ml concentrated hydrochloric acid, then heated for 2 hours under reflux and worked up as in Example 1. Colourless crystals of melting point 169 to 170°C [acetone]; R_f 0.30 [$CHCl_3/CH_3OH$ (7/3)]; yield 30.3 g (65%).

$C_{26}H_{28}BrNO_2$ (466.4)	Calculated	C 66.95	H 6.05	N 3.00
	Found	C 66.71	H 5.88	N 3.02

Molecular Weight 465 * (determined by mass spectrometry)

IR-Spectrum (KBr) γ(O-H) 3600 to 2400 cm^{-1}

^{1}H-NMR-Spectrum (d_6-DMSO) :

0.83	t (3)	$\underline{CH}_3$	[J=7.0]
2.23	s (6)	$(\underline{CH}_3)_2N$	
2.30 to 2.73	m (4)	$\underline{CH}_2$ and $\underline{CH}_2N$	
3.93	t (2)	$\underline{CH}_2O$	[J=6.0]
6.50 to 7.60	m (12)	Aromatics-$\underline{H}$	
9.43	s (1)	$O\underline{H}$ [interchangeable with D_2O]	

* Molecular weight with Bromisotope 79.

Example 4

Medicament containing (E)-1-[4'-dimethylaminoethoxy)phenyl] 1-(3'-hydroxyphenyl)-2-(3'-methylphenyl)-but-1-ene-hydrochloride.

21.82 g powdered (E)-1-[4'-(2-dimethylaminoethoxy)phenyl] -1-(3'-hydroxyphenyl)-2-(3'-methylphenyl)-but-1-ene- hydrochloride are blended with 40 g lactose and 140 g starch, then mixed with 33 g talc and 13 g calcium stearate, and after careful thorough mixing, the mixture is filled into two thousand hard gelatine capsules of suitable size so that each capsule contains 10 mg active ingredient (calculated as free base).

Example 5

Medicament containing
(E)-1-[4'(2-dimethylaminoethoxy)phenyl] -1-(3'-hydroxyphenyl)-2-(4'-methoxyphenyl)-but-1-ene.

20.0 g finely powdered (E)-1-[4'-(2-dimethylaminoethoxy)phenyl] -1-(3'-hydroxyphenyl)-2-(4'-methoxyphenyl)-but-1-ene, after blending with 111 g mannite, 15 g maize starch and 6 g alginic acid, is granulated and the dried granulate after careful blending with 0.75 g methyl cellulose and 1.5 g magnesium stearate is compressed into one thousand tablets, so that each tablet contains 20 mg active ingredient.

Example 6

Production according to the invention of
(E)-1-[4'-(2-diethylaminoethoxy) phenyl] -1-(3'-hydroxyphenyl)-2-(4'-methoxyphenyl)-but-1-ene

For preparation of the N,N-diethyl-2-phenoxyethyl ammonium chloride, 117 g (1.8 Mol) potassium hydroxide and 94.1 g (1 Mol) phenol in 1 l ethanol are reacted with 172 g (1.0 Mol) 2-chloroethyl-N,N-diethylammonium chloride, as described above under a). Colourless crystals with a melting point of 136 - 137°C are obtained from isopropanol in a yield of 79 g. In an analogous manner to that described in b) above or in DE-PS 30 46 719, the 1-[4'-(2-diethylaminoethoxy)phenyl]-2-(4'methoxyphenyl)-1-[3'-(2-tetrahydropyranyloxy)phenyl] -butan-1-ol is prepared therefrom.

54.7 g (0.1 Mol) of the diastereomeric mixture of 1-[4'-(2-diethylaminoethoxy)phenyl] -2-(4'methoxyphenyl)-1-[3'-(2-tetrahydropyranyloxy)-phenyl] -butan-1-ol in 1 l ethanol are reacted with 30 ml conc. hydrochloric acid, then heated for 2 hours under reflux and worked up as described in Example 1. Colourless light-sensitive crystals of melting point 128° - 130°C (acetonitrile); R_f 0.46 [benzene, triethylamine (94/6)]; yield 7.6 g (20%).

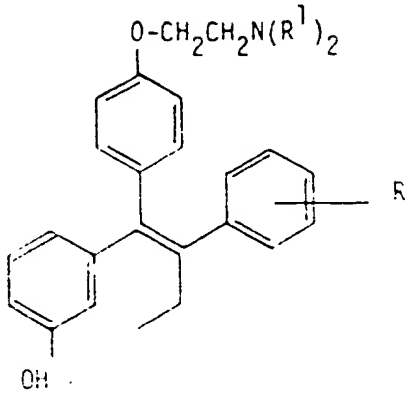
$C_{29}H_{35}NO_3$ (445.6)

Molecular weight 445 (determined by mass spectrometry)

^{1}H-NMR-Spectrum ($CDCl_3$) :	0.70 to 1.23	m	(9)	$3CH_3$
	2.23 to 2.97	m	(8)	$3CH_2N$ and $C{=}CCH_2$
	3.67 to 4.03	t		
	and 3.73	s	(5)	CH_2O and CH_3O
	6.27 to 7.30	m	(12)	Aromatics-H
	7.8	s	(1)	OH [interchangeable with D_2O]

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:-

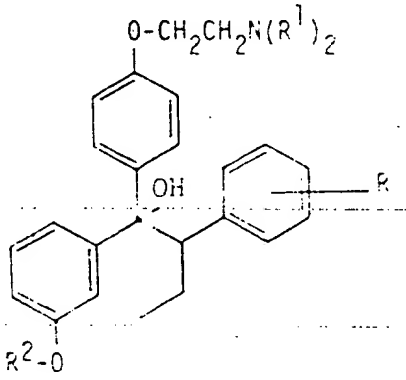
1. 1,1,2-triphenyl-but-1-ene derivatives of the general formula (1)



(1)

in which R is in position 3' or 4' and represents a methyl group, methoxygroup, hydroxy group or a halogen atom and R^1 represents a lower alkyl group; and therapeutically acceptable salts thereof.

2. Process for production of 1,1,2-triphenyl-but-1-ene derivatives according to claim 1, characterised in that carbinols of the general formula (2)



(2)

in which R in position 3' or 4' can be a methyl group, methoxy group, acetoxy group or easily hydrolysable group